ORGANIC
LETTERS

2004
Vol. 6, No. 23
4191−4194

Lithiation and Reactions of Stilbene Oxides: Synthetic Utility

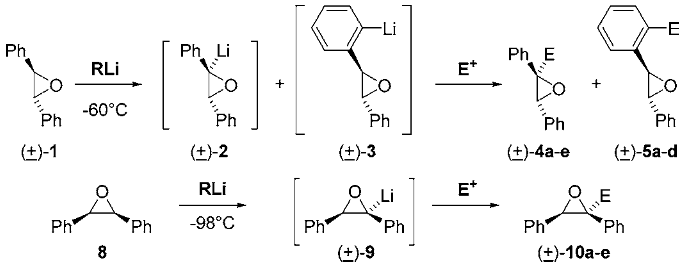
Saverio Florio,*[†] Varinder Aggarwal,*[‡] and Antonio Salomone[†,‡]

*Dipartimento Farmaco-Chimico, University of Bari, C.N.R.,
Istituto di Chimica dei Composti Organometallici "ICCOM",
Sezione di Bari, Via E. Orabona 4, I-70126-Bari, Italy, and
School of Chemistry, University of Bristol, Cantock's Close,
Bristol BS8 1TS, UK*

florio@farmchim.uniba.it; v.aggarwal@bristol.ac.uk

Received July 29, 2004

ABSTRACT



The lithiation of *trans*- and *cis*-stilbene oxides (±)-1 and 8 has been investigated. While with 8, lithiation occurred exclusively at the benzylic position, with the trans isomer (±)-1, ortho-lithiation competed with α-lithiation depending upon the experimental conditions. The configurational stability of the α-lithiated *cis*- and *trans*-stilbene oxides (±)-2 and (±)-9, respectively, was proved as well as that of scalemic stilbene oxide (*R*,*R*)-2.

Polysubstituted epoxides are often key intermediates in the construction of structurally complex molecules,[1] and as such their synthesis has been intensively studied.[2a−g] Among the numerous routes that have been developed to this end, the oxiranylanion-based methodology has been exploited in only a few cases.[2h] The related enantioselective version has been pursued even less.[2k,3,4]

Quite recently, we developed a new stereospecific synthesis of styrene oxide derivatives, which was based on the oxiranyllithium methodology. Starting from (*S*)- or (*R*)-styrene oxide, it was possible to obtain α-substituted styrene oxides in high yields and excellent enantiomeric purity.[3] The stereospecificity of the lithiation−trapping sequence of phenylpropylene oxides has also been shown.[4]

In continuation of our work on the chemistry of aryl-stabilized oxiranyllithiums, and to evaluate the substituent effect on their reactivity and stability, we conducted a detailed exploration of the lithiation of stilbene oxides and successive trapping with electrophiles.

[†] University of Bari, C.N.R., ICCOM.

[‡] University of Bristol.

(1) (a) Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T.; Thonyoo, P. *J. Org. Chem.* **2001**, *66*, 4692. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557. (c) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917. (d) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200. (e) Mori, Y. *Heteroat. Chem.* **1997**, *17*, 183. (f) Agami, C.; Dechoux, L.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 4071. (g) Dechoux, L.; Agami, C.; Doris, E.; Mioskowski, C. *Eur. J. Org. Chem.* **2001**, 4107. (h) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551.

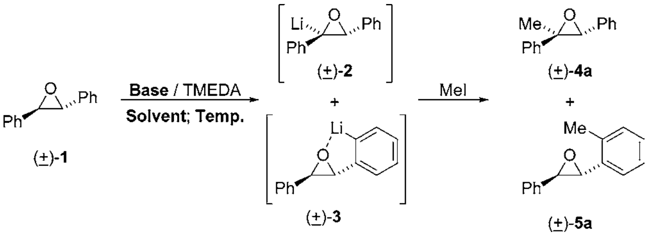
(2) (a) Kolb, H. C.; Sharpless, K. B. *Transition Met. Org. Synth.* **1998**, *2*, 219. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem.* **2001**, *113*, 1479. (d) Pedragosa-Moreau, S.; Morriseau, C.; Zylber, J.; Archelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 7402. (e) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone. A. *J. Org. Chem.* **2001**, *66*, 3049. For reviews see: (f) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885. (g) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611−620. (h) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625. (k) Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4* (2), 173.

(3) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.

(4) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330.

10.1021/ol0485013 CCC: $27.50

Scheme 1. Lithiation−Methylation of (±)-**1**



Lithiation of racemic *trans*-stilbene oxide **1** followed by quenching with MeI gave a mixture of the expected epoxide *trans*-**4a** and the ortho-methylated epoxide **5a**, the **4a**:**5a** ratio being dependent upon the experimental conditions (Scheme 1 and Table 1). *s*-BuLi (1.5 equiv), TMEDA (1.5 equiv), THF, −98 °C, and 1 h as the reaction time represented the best conditions for the formation of epoxide **5a** (**4a**:**5a** = 36:64, entry 6). To account for formation of **5a** we believe that there is coordinative assistance of the epoxide oxygen to the H−Li exchange on the phenyl ring (intermediate **3**). In other words, the epoxide is acting as an ortho-directing group (DoM methodology).[5] This behavior is quite surprising since benzylic ethers, unlike the related benzylic amines, usually undergo exclusive α-lithiation rather than ortho-lithiation.[6]

Table 1. Lithiation−Methylation of (±)-**1**: Effect of the Lithiating System and Experimental Conditions on the Regioselectivity[a]

entry	base (equiv)[b]	*T* (°C)	*t* (min)	**4a**:**5a**[c,d,e]	conversion of **1** (%)[c]
1	*s*-BuLi (2)[f]	−78	45	70:30	98
2	*s*-BuLi (2)[f,g]	−78	45	66:34	98
3	*s*-BuLi (2)[f]	−50	30	85:15	98
4	*s*-BuLi (2)	−78	30	50:50	90
5	*s*-BuLi (1.5)[h]	−60	60	74:26	82
6	*s*-BuLi (1.5)[h]	−98	60	36:64	67
7	*s*-BuLi (1.1)	−98	30	37:63	48
8	*s*-BuLi (1.5)	−98	10	36:64	36
9	*n*-BuLi (3)	−60	120	92:8	88
10	*n*-BuLi (1.5)	−60	180	90:10	85
11	*n*-BuLi (1.5)[h,i]	−55	35	85:15	85
12	*n*-BuLi (1.5)	−60	120	90:10	81
13	*n*-BuLi (1.5)	−60	60	90:10	55
14	*n*-BuLi (3)[f]	−60	120	>98:2	40
15	*n*-BuLi (1.5)[h,j]	−55	35	85:15	34
16	*t*-BuLi (1.2)[f]	−78	60	>98:2	22
17	MeLi (1.5)[f]	−55	35	−	−
18	LDA (1.5)[f]	−98	15	−	−

[a] Reactions performed in THF/TMEDA (3 equiv). [b] Equivalents with respect to **1**. [c] Determined by ^{1}H NMR analysis. [d] For spectroscopic data of **4a** and **5a**, see ref 8. [e] Inseparable mixture. [f] Reaction without TMEDA. [g] Reaction in 2/1 hexane/THF. [h] Reaction performed with 1.5 equiv of TMEDA. [i] Reaction in toluene. [j] Reaction in DME.

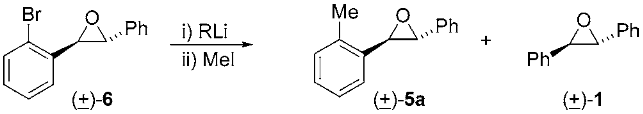
We made several attempts to increase the regioselectivity in favor of the ortho-lithiation by using different bases, lower temperatures (−110 to −98 °C), and different solvents: all were unsuccessful. The percentage of *trans*-**4a**, which was the minor product at −98 °C when using *s*-BuLi, increased with temperature until it became the main product at −60 °C (**4a**:**5a** = 74:26, entry 5). The conversion of starting material also increased with the temperature. When *trans*-**1** was lithiated (*s*-BuLi/TMEDA, −98 °C) and then allowed to warm to rt, PhCH$_2$COPh formed (75% yield) after acidic quenching. Such an isomerization of **1** has been already reported.[7]

We subsequently focused on finding conditions that favored α-deprotonation. Lithiation of **1** with either 3 or 1.5 equiv of *n*-BuLi and 3 equiv of TMEDA in THF at −60 °C for 2 h gave the best conversion of **1** to **2** with high regioselectivity. Quenching with MeI gave the α-substituted product **4a** in very good yields (81 and 73%) and high regioselectivity: the **4a**:**5a** ratio ranged from 92:8 to 90:10 (Table 1, entries 9 and 12).

An increase in regioselectivity was also observed (**4a**:**5a** > 98:2) when the deprotonation was performed without TMEDA, but the conversion of **1** was poor (40%) (Table 1, entry 14). Good yield and regioselectivity were also noted in toluene (entry 11). In all cases, the conversion of **1** to **4a** proceeded with complete retention of configuration.

We suspected that the observed temperature dependence in the regioselective lithiation of **1** could be the result of an equilibration of the α- and ortho-lithiated species ("anion translocation").[9] However, three experiments ruled out such a possibility. In the first, we subjected the *o*-bromo-*trans*-stilbene oxide **6**[10] to a lithiation−methylation sequence under a variety of experimental conditions. In no case did we observe α-methylation: only *trans*-**1** and the ortho-methylated compound **5a** were obtained (Table 2). The formation of **1** and **5a** can be ascribed to Li−Br exchange and hydrogen trapping by any proton source in the reaction medium and methylation with MeI, respectively.

Table 2. Reaction of Lithiated (±)-**6** in THF with MeI



RLi	time (h)	temp (°C)	**5a** (%)[a]	**1** (%)[a]
t-BuLi	1.5	−98	68	32
n-BuLi	1.5	−78	77	23
n-BuLi	0.5[b,c]	−78	72	10

[a] Yield by ^{1}H NMR analysis on the crude mixture. [b] Formation of **1** is lowered by shorter reaction times. [c] ^{1}H NMR analysis on the crude mixture showed 18% of unreacted (±)-**6**.

---

(5) *Organolithiums: Selectivity for Synthesis*; Clayden, J., Ed.; Pergamon: Oxford, 2002; Tetrahedron Organic Chemistry Series, Vol. 23, pp 28−73.

(6) Schoolkopf, U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 763.

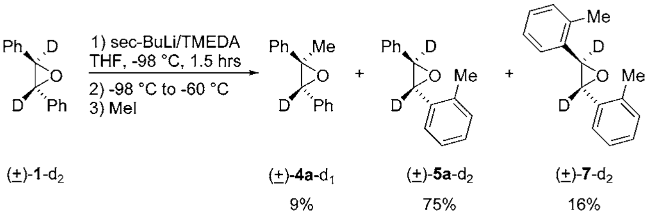
(7) Cope, A. C.; Trumbull, P. A.; Trumbull, E. *J. Am. Chem. Soc.* **1958**, *80*, 2844.

(8) Oudeyer, S.; Léonel, E.; Paugam, J. P.; Nédélec, J. Y. *Synthesis* **2004**, 389.

In the second experiment, *trans*-**1** was first lithiated with *s*-BuLi/TMEDA at −98 °C, kept there for 1.5 h, then warmed to −60 °C for 1 h and quenched with MeI. The **4a**:**5a** ratio was 57:43, which lies between the **4a**:**5a** ratio of 36:64 measured at −98 °C and 74:26 recorded at −60 °C. This result confirms that ortho-lithiation is favored at low temperature and α-lithiation at high temperature.[11]

In the third experiment, dideutero stilbene oxide **1**-d_2[12a] was first deprotonated with *s*-BuLi/TMEDA at −98 °C, warmed to −60 °C for 1.5 h, and then quenched with MeI to give *o*-methyl stilbene oxide **5a**-d_2, *o,o′*-dimethyl stilbene oxide **7**-d_2[12b] and α-methyl stilbene oxide **4a**-d_1 (Scheme 2).

Scheme 2. Reaction of Lithiated (±)-**1**-d_2 in THF with MeI

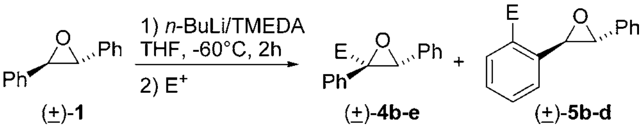


None of these products were ortho-deuterated, thus demonstrating the absence of ortho-lithiation followed by anion translocation to the α-lithio species. Interestingly, the regioselectivity (highly shifted toward ortho-lithiation) of the deprotonation−methylation sequence was highly dependent on the H/D substituent, thus demonstrating a remarkable kinetic isotopic effect. The deprotonation−methylation sequence carried out on the "light" stilbene oxide **1** led to a **4a**:**5a** ratio = 57:43, and the *o,o′*-dimethylated stilbene oxide **7** did not form at all.

Lithiation of **1**, carried out under conditions that favor α-deprotonation, followed by trapping with EtI and allylBr, afforded epoxides **4b** and **4c**, respectively, with high regioselectivity and complete retention of configuration, together with small amounts of epoxides **5b** and **5c**. Trapping with benzaldehyde, however, furnished epoxy alcohol **4d** (almost 1:1 diastereomeric mixture, dr = 60:40) together with epoxide **5d** (mixture of diastereoisomers, dr = 60:40) (Table 3).

The configuration of the two diastereoisomers of **4d** (1*R**,2*S**,3*R** and 1*R**,2*R**,3*S**) was deduced by 500 MHz ^{1}H NMR analysis.[13a] The configuration of **4d**-*syn* was also confirmed by X-ray analysis.[13b] Lithiation of **1** followed by quenching with PhCONMe$_2$ produced exclusively epoxide **4e** (Table 3, entry 4). These results provide further evidence of the configurational stability of the parent lithiated oxirane when held at −60 °C for 2 h.

Table 3. Reaction of Lithiated (±)-**1** with Electrophiles



entry	product	electrophile	E	**4** (%)[a]	**4**:**5**[b]
1	**4b**[c]	EtI	Et	57	97:3
2	**4c**[c]	AllylBr	Allyl	55	93:7
3	**4d**[e]	PhCHO	PhCHOH	56[d]	90:10
4	**4e**[e,f]	PhCONMe$_2$	PhCO	56	>99:1

[a] Isolated yields. [b] Regioisomeric ratio by ^{1}H NMR analysis on the crude mixture. [c] For spectroscopic data of **4b** and **4c**, see refs 8 and 14, respectively. [d] Overall yield in both diastereomers (dr = 60/40). [e] For spectroscopic data, see Supporting Information. [f] *s*-BuLi was used instead of *n*-BuLi to avoid the formation of PhCOBu by the reaction of *n*-BuLi with PhCONMe$_2$.

On the basis of results collected in Tables 1−3, the following conclusions can be drawn. First, the base used controls the regioselectivity of the deprotonation reaction, *s*-BuLi promoting ortho-lithiation, *n*-BuLi favoring α-lithiation. In all cases, addition of TMEDA promotes ortho-lithiation but to different extents depending on the base employed. Second, attempts to lithiate **1** with *t*-BuLi or LDA at −78 °C or lower temperature failed. In fact, just traces of **4a** and **5a** could be observed in the crude reaction mixture by ^{1}H NMR analysis after quenching with MeI (Table 1), although it had been reported that lithiated stilbene oxide **2**, generated upon treatment of **1** with *t*-BuLi (or LDA), could be trapped with Me$_3$SiCl (internal quenching).[15] Third, the regioselectivity depends also upon the electrophile, the addition of PhCONMe$_2$ to a mixture of *n*-BuLi, TMEDA, and **1** (Table 3, entry 4) furnishing the α-acyl stilbene oxide **4e** in a highly regioselective manner. NMR analysis of the crude reaction product did not show any trace of the acylated epoxide on the ortho position. This behavior may be due to a higher kinetic nucleophilicity of the oxiranyllithium **2** compared with the aryllithium **3**. Moreover, under the experimental conditions that favor the α-lithiation [*n*-BuLi (1.5 equiv), TMEDA (3 equiv), PhCONMe$_2$ (1.5 equiv) at −60 °C], 1-phenylpentanone (formed by addition of the excess *n*-BuLi to PhCONMe$_2$) might protonate the lithiated

---

(9) As an example of "anion translocation", see: Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett*. **1998**, *39*, 6103.

(10) For the preparation of **6**, see: Akgun, E.; Glinski, M. B.; Dawan, K. L.; Durst, T. *J. Org. Chem*. **1981**, *46*, 2730.

(11) Lithiation at −98 °C was not complete. Therefore, as the mixture is warmed from −98 to −60 °C, the remaining strarting material is deprotonated at the higher temperature, which favors α-lithiation.

(12) (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (b) The presence of **7**-d_2 (not isolated) was ascertained by ^{1}H NMR, GC-MS analysis on the crude mixture, and comparison with the light compound **7** (see Supporting Information).

(13) (a) According to previous observations on many diastereomeric epoxy alcohols (See ref 3 and: Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203), the carbinol proton of the syn isomer (in our case corresponding to (1*R**,2*S**,3*R**)-**4d**) absorbs at a lower field than the corresponding proton of the anti isomer (δ 4.81 vs 4.60 for **4d**-*syn* and **4d**-*anti*). (b) CCDC 246147 contains the supplementary crystallographic data for compound (1*R**,2*S**,3*R**)-**4d**. These data can be obtained free of charge via the Internet at www.ccdc.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (int) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk.

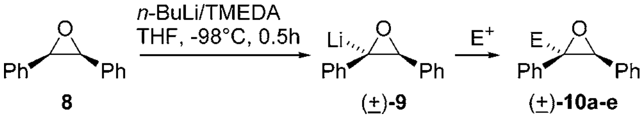
(14) Yano, K.; Hatta, Y.; Baba, A.; Matsuda, H. *Synthesis* **1992**, 693.

(15) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835−4840 and refs cited therein.

species **2** and **3**: in fact, only 10% of **4e** was observed. In that case, the use of *sec*-BuLi was necessary to obtain **4e** in 56% yield.

We next studied the lithiation of *cis*-stilbene oxide **8**. It was interesting to observe that, in this case, the α-lithiation *versus* ortho-lithiation competition does not take place. Indeed, when MeI was added to the lithiated *cis*-stilbene oxide **9** [generated by deprotonation of **8** (*n*-BuLi (1.5 equiv)/TMEDA (3.0 equiv), THF, −98 °C, 30 min)], the α-methylated compound **10a** was formed exclusively. The absence of ortho-lithiation may reflect the reduced steric hindrance associated with α-lithiation of *cis*-stilbene oxide compared to the trans isomer. The higher reactivity of *cis*-epoxides toward deprotonation with respect to the trans isomers is well documented.[16] Similarly, treatment of **9** with other electrophiles (Table 4) produced exclusively the α-functionalized stilbene oxides **10a−e** again with complete retention of configuration. To understand the fate of lithiated *cis*-stilbene oxide **9** at temperatures higher than −98 °C, we deprotonated **8** with *n*-BuLi/TMEDA in THF at −98 °C and allowed the reaction mixture to reach room temperature. The major product was $PhCH_2COPh$ (62% yield).

Table 4. Reaction of Lithiated **8** with Electrophiles

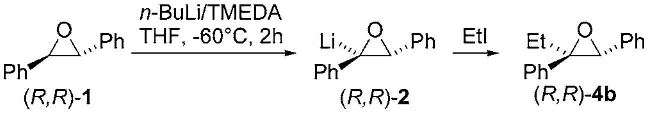


entry	product	electrophile	E	yield (%)[a]
1	**10a**[b]	MeI	Me	89[c]
2	**10b**[b]	EtI	Et	76
3	**10c**[d]	AllylBr	Allyl	55[e]
4	**10d**[f,g,h]	PhCHO	PhCHOH	91[i]
5	**10e**[f]	$PhCONMe_2$	PhCO	88

[a] Isolated yields. [b] For spectroscopic data of **10a** and **10b** see ref 8. [c] Yield by ^{1}H NMR analysis. [d] For spectroscopic data of **10c**, see ref 14. [e] 1,2-Diphenyl ethanone was isolated in 40% yield (oxiranyllithium isomerization product). [f] For spectroscopic data, see Supporting Information. [g] Inseparable mixture of diastereoisomers; the separation and subsequent full characterization was possible only on the *O*-acetyl derivatives. [h] Relative configuration of the two diastereoisomers (syn and anti, respectively, (1*R**,2*S**,3*S**)-**10d** and (1*R**,2*R**,3*R**)-**10d**) was assigned by ^{1}H NMR.[13a] [i] Overall yield in both diastereomers (dr = 70:30).

We also studied the lithiation of scalemic (*R*,*R*)-*trans*-stilbene oxide **1** (ee = 98%)[12] (Scheme 3). Treatment of (*R*,*R*)-**1** with *n*-BuLi at −60 °C gave the lithiated derivative (*R*,*R*)-**2**, which proved to be quite stable and could be kept for at least 2 h at that temperature. Quenching with EtI furnished (*R*,*R*)-*trans*-stilbene oxide (+)-**4b** ($[\alpha]_D = +22$ (*c* 0.93, $CHCl_3$) (45% yield) together with the starting epoxide (*R*,*R*)-**1** (27%). The ^{1}H NMR analysis of (+)-**4b** showed no signal of the cis epimer.

Scheme 3. Lithiation−Ethylation of (*R*,*R*)-**1**



In conclusion, α-lithiated stilbene oxides **2** and **9** proved to be chemically much more stable than lithiated styrene oxide.[3] Indeed, **2** and (*R*,*R*)-**2** can be kept at −60 °C for at least 2 h and **9** at −98 °C for 30 min. Moreover, due to their configurational stability, it is possible to trap the α-lithiated stilbene oxides, in a stereospecific manner, by alkylation, hydroxyalkylation, or acylation of the benzylic position. We have also observed, for the first time to our knowledge, the ortho-directing capability of the oxirane moiety in lithiation of the phenyl ring. Finding experimental conditions that favor the ortho-lithiation is at present being pursued in our labs. Further studies are under way to exploit the configurational stability of lithiated stilbene oxides.

Acknowledgment. We thank MIUR (Rome) and the University of Bari for financial support to National Project "Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni" and the FIRB Project. We are also grateful to Dr. Michel Giorgi of the Faculté des Sciences Saint-Jerome, Marseille, France, for performing X-ray analysis of compound (1*R**,2*S**,3*R**)-**4d**. We also thank the University of Bristol for hosting Ph.D. Antonio Salomone.

Supporting Information Available: Full experimental details and characterization data (^{1}H and ^{13}C NMR, physical data) for compounds **4b**, **4d−e**, **7**, and **10a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0485013

---

(16) Molander, G. A.; Mautner, K. *Pure Appl. Chem.* **1990**, *62*, 707.